WASHINGTON UNIVERSITY

SCHOOL OF MEDICINE
SAINT LOUIS (10)

DEPARTMENT OF BACTERIOLOGY AND IMMUNOLOGY
EUCLID AVENUE AND KINGSHIGHWAY

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Dear Josh:

In attempting to answer the questions raised in your last letter of November 14th I found that I was duplicating a manuscript that I wrote some time ago and delivered last summer at a place called Cold Spring Harbor. That being the case, and to save time and effort, it seemed best to send you the pertinent portion for your careful study which latter, I might add, I expect to see returned at your convenience.

The enclosure.

All kidding aside, I really believe that I have answered the questions which you have raised, but I believe that in order to see it, you must put yourself in a more biological frame of mind and really think about competitive interaction on a biological level. I should note that I do not specify at what level the competition between the enzyme-forming systems exists. I have no information on that. All we know is that competition for protein takes place. The effect of azide is merely one of blocking energy supply to all the synthetic reactions, which means the complete cessation of all competitive interaction. Thus, if the instability of any given enzyme is primarily due to competitive relations with other enzyme-forming systems, the addition of azide will completely stabilize it, and it is not due to any effect on the velocity constants of the precursor to enzyme transformation. It implies only that the back-reaction in the absence of competition is very low and indeed, almost negligible. In other words, both the backward and forward reaction velocity constants leading from precursor to enzyme are functions of the amount of protein transformation that is going on, as well as available supply of protein for enzyme formation. It is for this reason that the velocity constant is affected by azide and not because the azide actually interacts with that step specifically.

I hope this will make clear in your mind my concept of what is going on here. It is apparently a difficult one for me to get over since if you do not understand it, I have great doubts about many other people.

With reference to the experiments that you mention, Hershey and I simply tried to see, not too critically I must add, whether the addition of lactose to the medium leads to an apparent depression in the mutation away from lactose fermentation. Unfortunately, we were not successful in

obtaining a mutant which mutated rapidly enough in this direction, but the ones which we did try did not give very encouraging results. Now as far as your own experiments are concerned, I should like to point out that it is not reasonable to expect that the addition of lactose would necessarily lead to the disappearance of all Lac- phenotypes. The best that one can hope for is that some of them are positive phenotypically but not genotypically. Now how you could test that is a little difficult to see, since your crosses, world-shaking as they are in implications, are not as yet adequate for a Mendelian analysis of the segregation of bacterial characters.

One other point I find surprising. You say that a few Lac + were tested for stability of fermentative character after growth on lactose-deficient medium. I should be very interested in learning more details about this experiment since both Monod and myself independently found quite different results; that is to day, that the growth in a lactose-deficient medium of Lac+ strains invariably led to loss of ability to ferment lactose but not loss of ability to adapt to lactose fermentation, and I should like to know in particular how you tested for the fermentative character, that is to say, did you simply grow them in lactose medium or did you test manometrically, or what?

Finally, I should like to note this. It is apparent from experiments which have been going on for some time that substrate is not the ~~sine qua non~~ sine qua non* of cytoplasmic transfer. It can occur in its absence and furthermore, its presence does not invariably guarantee it. Our own work has taken a very happy turn at the moment. We believe that we have cracked the adaptin problem wide open at the moment, with some very surprising and comforting results. I unfortunately cannot reveal them yet as some further work still remains to be done.

However, I feel sure that by some mysterious and, to me, incomprehensible means, these results will become known to you, modified possibly in a few essential details through the remarkable rumour factory which is apparently so over-active on the eastern seaboard. In connection with this, I should like to note that I have not transformed a raffinose non-adapter to a raffinose adapter. In fact, I have never had raffinose in my laboratory. To put the thing straight so that at least the proper sugar is mentioned, in future rumours, I will say that we are trying to transform maltose non-adapters.

Sincerely yours,

Sol

S. Spiegelman

ss/b

* This is even ~~better~~ apparent in our first paper on "Mendelian Segregation of Melibiose."